

**REMARKS**

Claims 1-3, 5, 6, 14, and 15 are pending in the application.

Claims 2, 4, 7-13, 16-67 have been cancelled without prejudice.

Claims 1, 3, 14 and 15 have been amended.

**I. Amended Claims 1, 3, 14 and 15.**

Although claim 1 was objected to because there was no "semicolon" after the phrase "the group consisting of", Applicants are unaware of any rule requiring specific punctuation after this phrase. Applicants submit that placement of a semicolon after this phrase would be improper. The claim is perfectly clear without a semicolon. However, in the interest of expediting prosecution of the application, claim 1 has been amended to add a colon after the quoted phrase. Applicants believe that placement of a colon after the phrase "consisting essentially of" should clarify any possible perception of ambiguity in the claim. The phrase "corresponding to" has also been changed to "consisting of" to address the Examiner's rejection under the second paragraph of 35 USC §112.

Claim 3 has been amended to change "cRaf" to "c-Raf" for consistency with claim 1. In addition, claims 14 and 15 have been amended to clarify that the functional language in the claim constitutes written matter on the label, as opposed to a method step.

No new matter is added by any of these amendments.

**II. Claims 1, 2, 5, 6, 14, and 15 are not obvious over Freed *et al.* or the combination of Freed *et al.* and Przybyszewska *et al.***

Claims 1, 2, 5, 6, 14, and 15 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Freed *et al.* or the combination of Freed *et al.* and Przybyszewska *et al.* In order to establish a *prima facie* case for obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974). That is not the case here. Additionally, "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970).

Freed *et al.* is directed to complexes of Raf-1 (c-Raf) and human 14-3-3 proteins and to methods for identifying novel drugs that modulate Raf-1 activity *in vivo* (see Abstract and claims). Freed *et al.* discloses the structure of Raf-1 protein and various fragments thereof and

interactions between these proteins and human 14-3-3 proteins.

The present claims are directed to articles of manufacture, not to pharmaceutical compositions, not to specific Raf compounds, not to methods. The articles of manufacture of the present claims must include the following components:

1. packaging material;  
2. a pharmaceutical composition capable of stimulating angiogenesis within the packaging material, which includes at least about 0.1 weight percent of a compound selected from:

- (a) c-Raf,
- (b) residues 306-648 of c-Raf, and
- (c) Raf-caax,

in a physiologically acceptable excipient or carrier; and

3. a label containing specified printed matter setting forth instructions and directions for use of the composition.

Freed *et al.* do not teach or suggest all of the limitations of the presently claimed articles of manufacture. In particular they do not teach or suggest at least about 0.1 % by weight of the specific active Raf proteins contained within packaging material that has a label affixed thereto. Nor do Freed *et al.* teach or suggest that the Raf proteins stimulate angiogenesis, which is the subject matter of the writing on the label. Accordingly, this reference, alone, cannot render claim 1 obvious, since it does not teach or suggest all of the limitations of the claim.

The Office Action indicates that printed words on a label cannot be given patentable weight unless the article is changed by the written matter. Applicants respectfully submit that this is precisely the case with the present claims. Obviousness is determined at the time the invention was made. In the present case, one of ordinary skill in the art would not have been able to use the claimed articles of manufacture to stimulate angiogenesis, since this concept was unknown to one of ordinary skill in the art at the time the invention was made. In claim 1, the printed matter on the label should be given patentable weight because the instructions and information on the label impart specific functionality to the article of manufacture that was previously unknown to one of ordinary skill in the art. The printed matter would distinguish the

claimed articles of manufacture from other articles containing such a composition, were such article to have been known in the art. Furthermore, the information on the label *vis-a-vis* the ability of active Raf proteins to stimulate angiogenesis is novel and informs the user of the article how the article is to be utilized. This label limitation is analogous to the situation in *Miller* where the item at issue was a measuring cup. Without the printed matter, the cup had a utility of its own. With the printed matter, the measuring cup had a new and distinct utility (facilitating the preparation of fractional portions of a recipe without the need for mathematical calculations). The printed matter was specifically claimed to be "on" the cup, and this sufficed to provide the structural relationship necessary to carry out the invention. See *In re Miller*, 164 USPQ 46, 49 (CCPA 1969):

"... printed matter, in an article of manufacture claims, can be given patentable weight ... no attempt is here being made to patent printed matter as such. The fact that printed matter by itself is not patentable subject matter, because non-statutory, is no reason for ignoring it when the claim is directed to a combination ... The solicitor seems to urge that we ignore the claim limitations to the legends because they are printed and because printed matter is not patentable subject matter by itself ... we reject that argument."

Applicants take exception to the Examiner's comments that *Miller* and *In re Gulack* are not applicable here. In *Miller*, prior to adding the printed matter onto the measuring cup, that cup had utility as a simple cup. The new printed matter on the cup conveyed a new utility not previously known to one of ordinary skill in the art. Similarly, *In re Gulack*, 217 USPQ 401, 403 (CCPA 1983) involved a band imprinted with a series of digits derived from a mathematical algorithm. The band could be a hat band, for example, having utility on its own. Before the application of the printed matter, the band could be used as a hat band, or for other purposes. Adding the new printed matter onto the band conveyed a new utility that was not previously known to one of ordinary skill in the art, i.e., it was now useful for performing "magic tricks" and for displaying various aspects of number theory. The CCPA found that the band supported the numbers and the numbers had a relationship to each other that provided a new utility to the band.

Clearly, in the present claims, the printed matter conveys a new utility to an

article of manufacture that was not known in the prior art. Furthermore, while the compounds may have been known, their inclusion in packaging material in the specified amounts with a label, as an article of manufacture, was not known and is not taught or suggested by Freed *et al.* Accordingly, the present claims are patentable over this reference.

Przybyszewska *et al.* is directed to angiogenesis induced by urothelial cells that have been transformed by v-Ras and v-Raf, not c-Raf or fragments of c-Raf. This reference does not teach or suggest that c-Raf or its fragments, as isolated materials, can stimulate angiogenesis. Neither this reference nor Freed *et al.* nor the combination thereof teaches or suggests that c-Raf or its fragments have utility in a pharmaceutical composition or in an article of manufacture containing such a composition.

In addition, Przybyszewska *et al.* is directed to v-Raf and v-Ras transfected cells not to Raf-1 (c-Raf)-containing compositions as is Freed *et al.* One of ordinary skill in the art would not have been motivated to combine the teachings of these two references, since they deal with different compounds and concepts (v-Raf transformed cells versus Raf-1/14-3-3 protein complexes. Moreover, the combined references do not teach or suggest the packaging material, the minimum level of 0.1% Raf protein, or the label with its included written matter. Accordingly, the present claims are patentable over this combination of references.

**III. Claims 1, 2, 5, 6, 14, and 15 are not obvious over Kolch *et al.* or the combination of Kolch *et al.* and Przybyszewska *et al.***

Claims 1, 2, 5, 6, 14, and 15 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Kolch *et al.* or the combination of Kolch *et al.* and Przybyszewska *et al.* These references do not render claim 1 obvious, either alone or in combination.

Kolch *et al.* describe preparation of human c-Raf expression vectors and transfection of cells with those vectors. This reference does not teach or suggest that c-Raf, *per se*, has utility in a pharmaceutical composition, nor does the reference teach or suggest an article of manufacture containing a minimum of 0.1% of c-Raf or its fragments in packaging material having a label including specific written matter affixed thereto. This reference does not teach or suggest all of the limitations of the claims.

The teachings of Przybyszewska *et al.* were discussed above. The combination of

Kolch *et al.* and Przybyszewska *et al.* also fails to teach or suggest all of the limitations of the claims. At best, the combination of these references might have motivated one of ordinary skill in the art to transfect a urothelial cell line with c-Raf to test whether c-Raf transfected cells behave like the v-Raf transfected cells of Przybyszewska *et al.* Such a combination would not have motivated one of ordinary skill in the art to construct the articles of manufacture specified by the present claims. No article of manufacture is suggested by this combination of references at all.

#### IV. Conclusion

Claims 1, 3, 5, 6, 14, and 15 meet all of the requirements of 35 U.S.C. §112 and are patentable over the applied art. Reconsideration of the rejections and early passing of this application to issue is earnestly solicited.

Respectfully submitted,

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By \_\_\_\_\_

  
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